

Werdnig-Hoffmann-Wohlfart-Kugelberg-Welander Disease

Nosological Unity and Clinical Variability in Intrafamilial Cases

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SUMMARY

Two members of an Italian family are affected with progressive spinal muscular atrophy. One, a male, has had the disease since his early infancy and, though severely disabled, is still living at the age of 13. In his sister, the first symptoms appeared at the age of 15, and the disease seems to be rapidly advancing. Their parents were consanguineous. Their mother, however, married twice, her second marriage being nonconsanguineous and producing no affected children.

The study of this family and an analysis of the literature led to the following conclusions: (a) early onset of the disease does not necessarily mean that the course will be malignant; (b) the disease usually has a similar onset and course in subjects belonging to the same family.

In many families, however (and these have been examined in the present paper) malignant Werdnig-Hoffmann disease is found to coexist with the Werdnig-Hoffmann disease with a prolonged course, the Wohlfart-Kugelberg-Welander disease with infantile onset, and the Wohlfart-Kugelberg-Welander disease with juvenile onset. We feel, therefore, that from a genetic point of view all these forms should be included into one and the same group.

A certain confusion still exists over the relationship between the Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander diseases, and over the nosological limits between the two.

Prior to the study by Wohlfart et al (1955) and, above all, before the paper by Kugelberg and Welander (1956), authors (cf. Radermecker, 1951) considered *Werdnig-Hoffmann disease as being characterized by muscular weakness and hypotonia with absence of deep tendon reflexes. It was often accompanied by slightly hollow breastbone. The disease was congenital; its onset, however, fell within the first months of life. Death frequently occurred during the first year, but some cases survived until the third and even the fourth year of life.*

Yet, Brandt (1950) and Adams et al (1962) maintained that cases which survived into adolescence and adult life should also be considered to be cases of Werdnig-Hoffmann disease. [“Exceptional patients lived on to adolescent or even adult years” (Adams et al, 1962)].

The age of onset, however, was not always confined to the first months of life.

Gurdjian (1930) reported having studied a family M. in which symptoms were present at birth in one case, at the age of 15 months in another, and at the age of 16 months in a third one (cases no. 2, 3, and 4).

Also in family XIV of Brandt's report (1950), the disease appeared in one subject at 7-8 months, and in his brother at 18 months of age.

Kugelberg and Welander (1956) pointed out the nosological autonomy of the disease affecting their patients. Yet, they reported cases in which onset occurred at the age of 10, 14, 15, and 17 years of age, as well as five cases with onset at 3, and one case with onset at 2 years of age.

Assuming that cases with prolonged survival and those with onset in the second year of life may be included into Werdnig-Hoffmann disease, the sole difference between the latter and Wohlfart-Kugelberg-Welander disease would be confined to a variance of a few months in onset. One of the two forms (Werdnig-Hoffmann) may appear at the age of 15-16-18 months (Gurdjian, 1930; Brandt, 1950) while the other one (Wohlfart-Kugelberg-Welander) may appear at the age of 24 months (Kugelberg and Welander: case no. 4, 1956).

Kugelberg and Welander (1956) pointed out in their patients a "progressive spinal muscular atrophy, simulating progressive muscular dystrophy" (main muscular atrophy involving limb girdles). Yet, the same has also been observed in patients with a prolonged course of Werdnig-Hoffmann disease (Hausmanowa-Petrusewicz et al, 1966).

It should also be mentioned that in the second case described by Werdnig (1891), muscular atrophy was present, involving at onset thighs, pelvis, and back muscles.

Case Material

FAMILY HISTORY (Fig. 1)

Our probands V-5 and V-6 are born from the consanguineous marriage of III-3 with his relative IV-8. Both siblings are affected with the disease. From their mother's subsequent marriage with a man without any family tie (IV-9) three healthy children were born (V-8, V-10, V-11) and two pregnancies were interrupted by abortion, one of which, however, was certainly induced.

Genetical investigation did not bring to light any information concerning neuromuscular disease in ancestors and relatives.

CASE NO. 1 (V-6: ♂, aged 13)

Admitted into the Clinic for Nervous and Mental Diseases, University of Naples, on August 4, 1969, and discharged on August 30, 1969.

In his case, gestation, labour, delivery, and neonatal course had been normal. He was breast-fed by his mother. Subsequent development was normal except for deambulation. He was able to walk unaided only at 2½ years. Gait was always difficult, particularly in climbing and descending stairs.

At the age of 5½ he had measles with a high temperature. During convalescence he

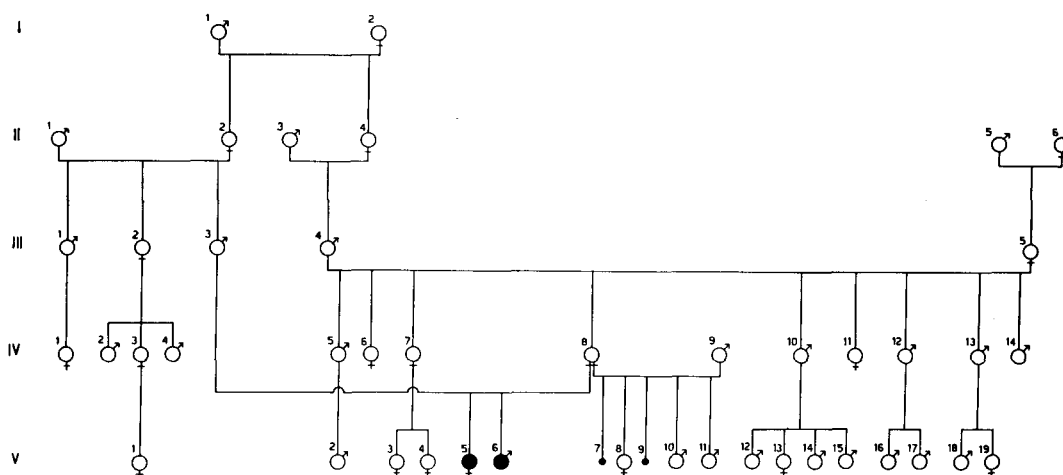


Fig. 1. The G. family. The two probands, affected with infantile-juvenile spinal muscular atrophy, were born from a woman's marriage with her father's first cousin. None of the three children born from the same woman's second nonconsanguineous marriage was affected.

began to feel weakness in his right lower limb. It further increased preexisting clumsiness in walking and lessened his ability to move about alone. The gradual reduction of strength was accompanied by the thinning of both lower limbs. These symptoms progressively increased up to the time when he was 11½. At that time, after getting over acute bronchitis with a very high temperature, he was no longer able to walk or stand upright unaided. Subsequently, he also felt a certain numbness and difficulty in extending and raising his lower limbs. His parents observed an increase in the thinning of his lower limbs, as well as an initial muscular volume decrease involving the upper limb girdle, after the above mentioned bronchitis.

EXAMINATION. The subject was severely disabled (Fig. 2), but generally well developed. Examination of the internal organs did not reveal any detectable malfunction.

NEUROLOGICAL EXAMINATION. The clinical picture showed above all marked diffuse atrophy; both lower limbs, and especially the right one, were severely wasted. The patient's knees were slightly bent and this position was unchangeable, because of muscular retraction. Muscular atrophy, though less evident, could furthermore be observed in both shoulder girdles. No fasciculation in the skeletal muscles or the tongue was observed. Moderate right-convex scoliosis was found in the dorsal tract of the spine. Standing upright and walking were impossible. There were no pathological findings as regards the cranial nerves. The muscular tone was reduced markedly, deep tendon reflexes were absent both in upper and lower limbs. Pyramidal and extrapyramidal signs were absent. The cerebellar examination seemed to be normal, consistently with the patient's ability to move. All sensory functions were intact. Examination revealed no remarkable psychopathological impairment. The patient's psychic evolution seemed to be in keeping with his age.

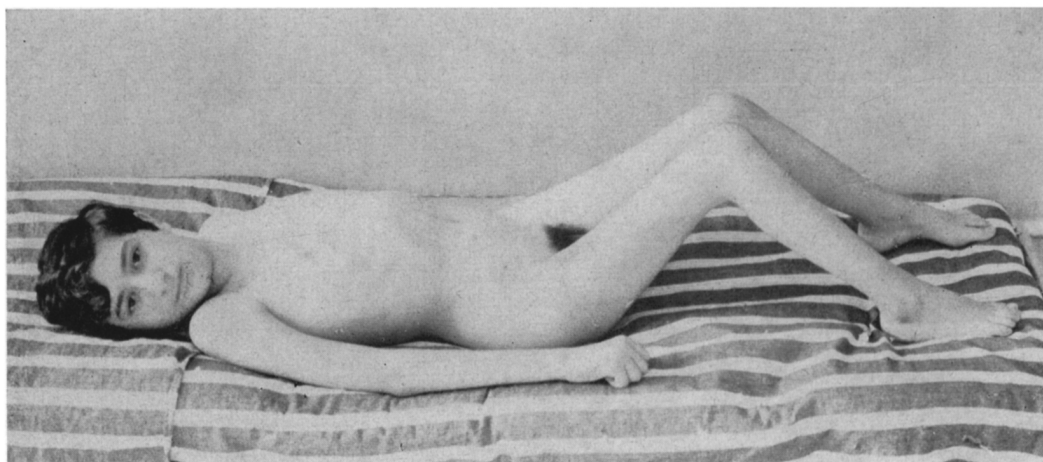


Fig. 2. Case No. 1: neuropathic muscular atrophy at an advanced stage

LABORATORY DATA

Blood: Azotemia $0.35 \text{ g}^0/_{00}$; Glycemia $0.70 \text{ g}^0/_{00}$; Serum transaminase: SGOT 42 U.I./l/37°C, SGPT 34 U.I./l/37°C; Aldolase 2.21 U.I./l/37°C; Lactic dehydrogenase 101 U.I./l/25°C.

Urine: Normal findings in routine examination. Screening examinations for aminoaciduria: Ferropchloride test negative; Dinitrophenylhydrazine test negative; Brand test negative; Sulphuric acid test negative; Electrochromatographic qualitative and semi-quantitative dosage of urinary aminoacids: normal excretion.

EEG (Prof. C. Paolozzi): no abnormalities, in keeping with the age of the patient.

EMG (Prof. G. Sanna): left tibialis anterior and right brachial biceps. On maximal contraction, reduced interference, giant potentials, increased duration of motor unit potentials, and polyphasy were observed. No spontaneous activity was present. Remarkable insertional activity (Fig. 3). *Conclusions:* Diffuse neuropathic affection. Injury of anterior horn motor neurons.

Biopsy: Skin normal. Sural nerve: deeply marked segmental demyelination associated with Schwann cells gliosis. Sural triceps: neuropathic, typical myoatrophy (Fig. 4, A and B).

CASE No. 2 (V-5: ♀, aged 16)

Normal gestation, labour, delivery, and neonatal course. She was breast-fed by her mother up to the 16th month of life. Subsequent physiological development was normal. She menstruated at 13, and following menstruations were regular. School performance was excellent.

At the age of 7 after getting over measles, she frequently felt tired and asthenic. She improved after undergoing undefined vitaminic treatment. No dysfunction was observed up to the age of 15. At that time she felt weakness in her lower limbs and she sometimes fell down. There has since been a gradual deterioration in her condition.

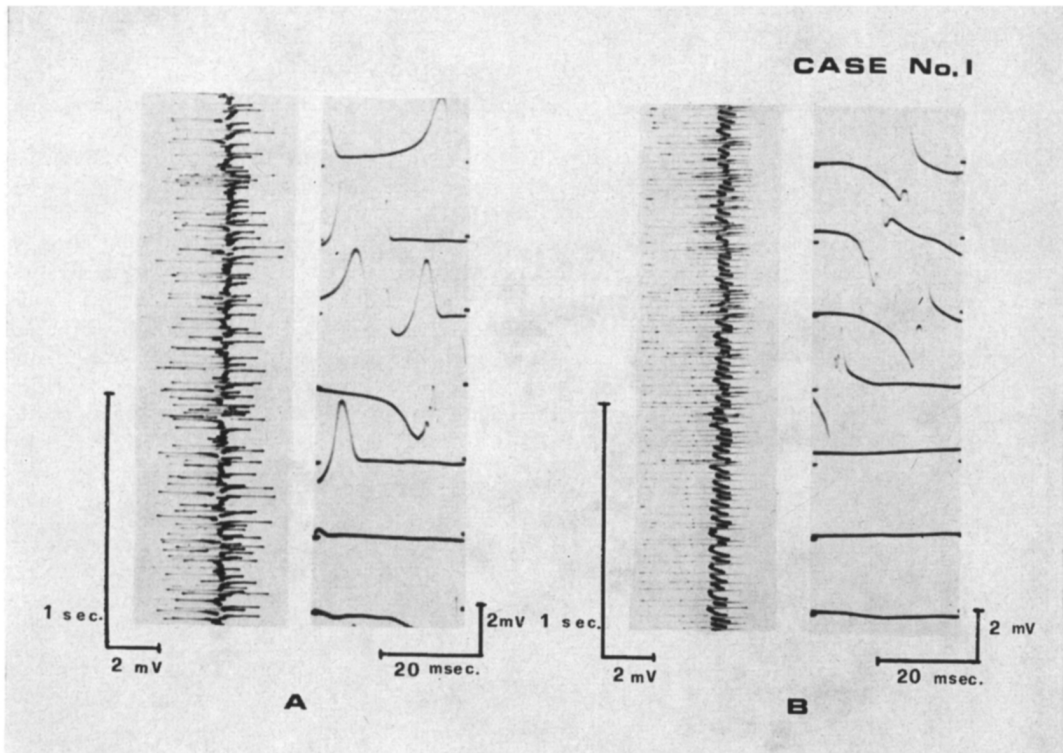


Fig. 3. Electromyographic recordings from left tibialis anterior (A) and right brachial biceps (B).
 Reduced interference on maximal contraction.
 Highly increased duration and amplitude of motor unit potentials.

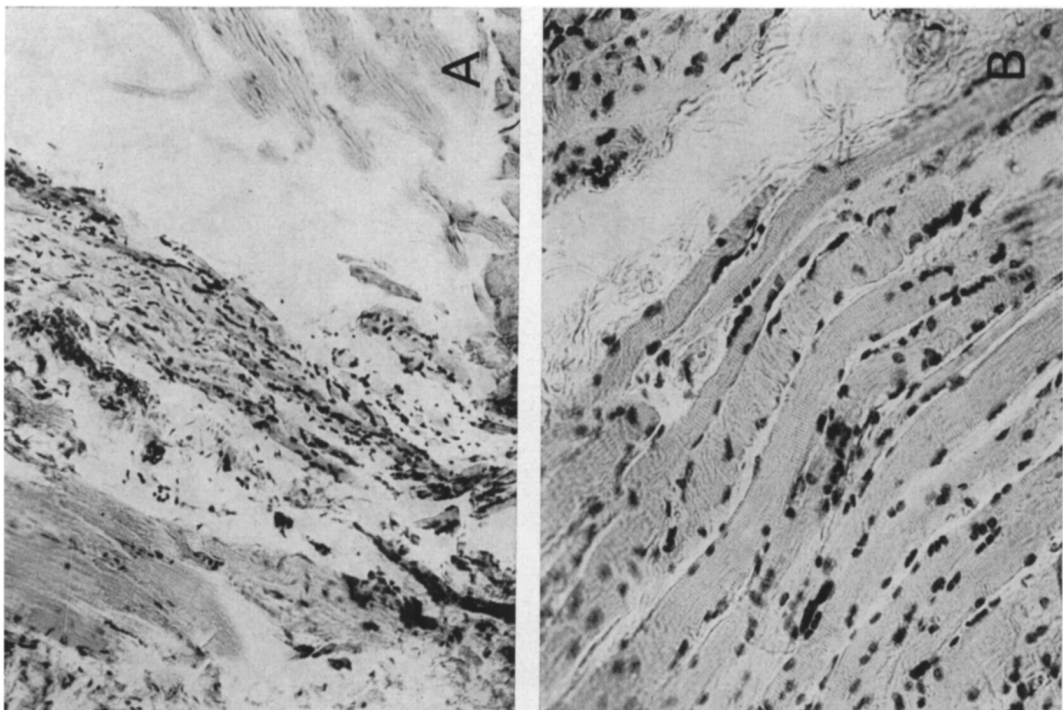


Fig. 4. A and B. Case No. 1: biopsy, sural triceps.
 Fields of atrophic fibers are observed beside fields of muscular fibers with normal form and volume.
 Single fibers having lost longitudinal and transverse striations.

CLINICAL EXAMINATION. The subject appeared to be in good general condition. Examination of the internal organs did not reveal any detectable malfunction.

NEUROLOGICAL EXAMINATION. Moderate, diffuse muscular atrophy was observed (Figs. 5 and 6). The patient stood upright normally and walked with her legs slightly apart. Findings were normal as regards the cranial nerves: moderate nystagmus was observed, however, when she looked to one side; it was more evident when she looked left. Marked hypotonia, slight, diffuse hyposthenia and hypotrophy were present both in the upper and lower limbs. Deep tendon reflexes were absent in the lower limbs. Feeble tricipital reflex was however still elicited in the upper limbs. The cutaneous plantar reflex was sluggish.

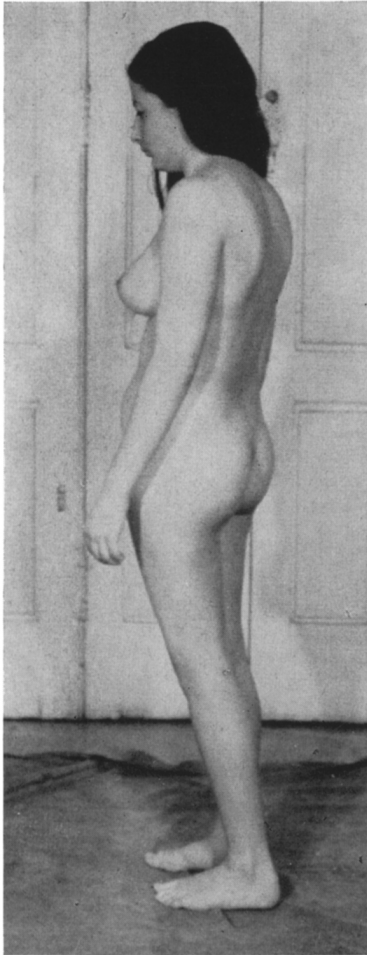


Fig. 5. Case No. 2:
moderate diffuse muscular atrophy

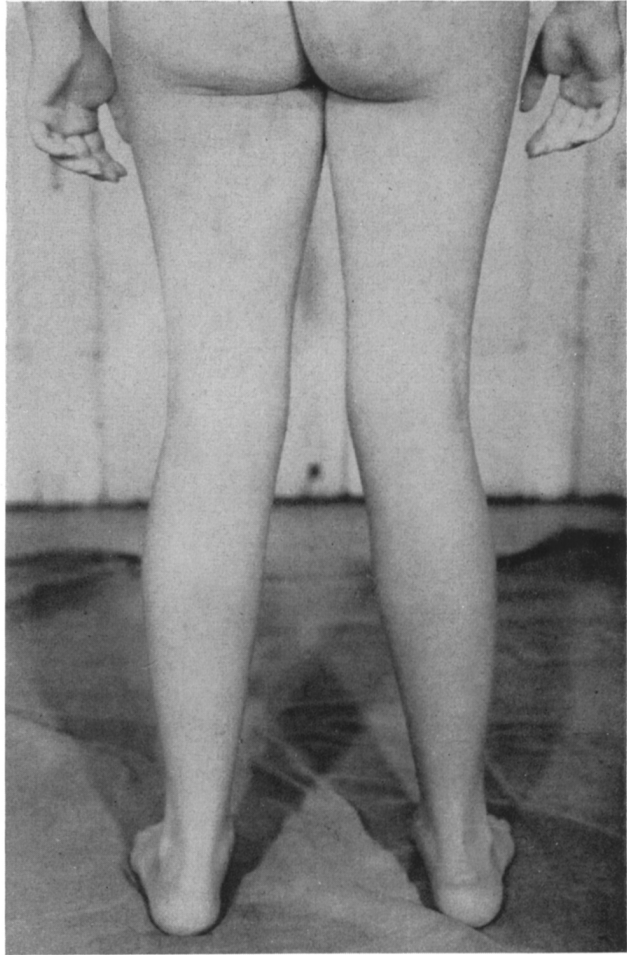


Fig. 6. Case No. 2:
atrophy involving all muscles of lower limbs

Abdominal reflexes were present and symmetrical. Cerebellar and extrapyramidal signs were absent. All sensory functions were intact. No psychopathological impairment was observed.

LABORATORY DATA

Blood: Azotemia 0.30 g^o/₁₀₀; Glycemia 0.90 g^o/₁₀₀; Serum transaminase: SGOT 67 U.I./l/37°C, SGPT 59 U.I./l/37°C; Aldolase 2.66 U.I./l/37°C; Lactic dehydrogenase 101 U.I./l/25°C.

Urine: Normal findings in routine examination. Screening examination for aminoaciduria: Ferropchloride test negative; Dinitrophenylhydrazine test negative; Brand test negative; Sulphuric acid test negative; Electrochromatographic qualitative and semiquantitative dosage of urinary aminoacids: normal excretion.

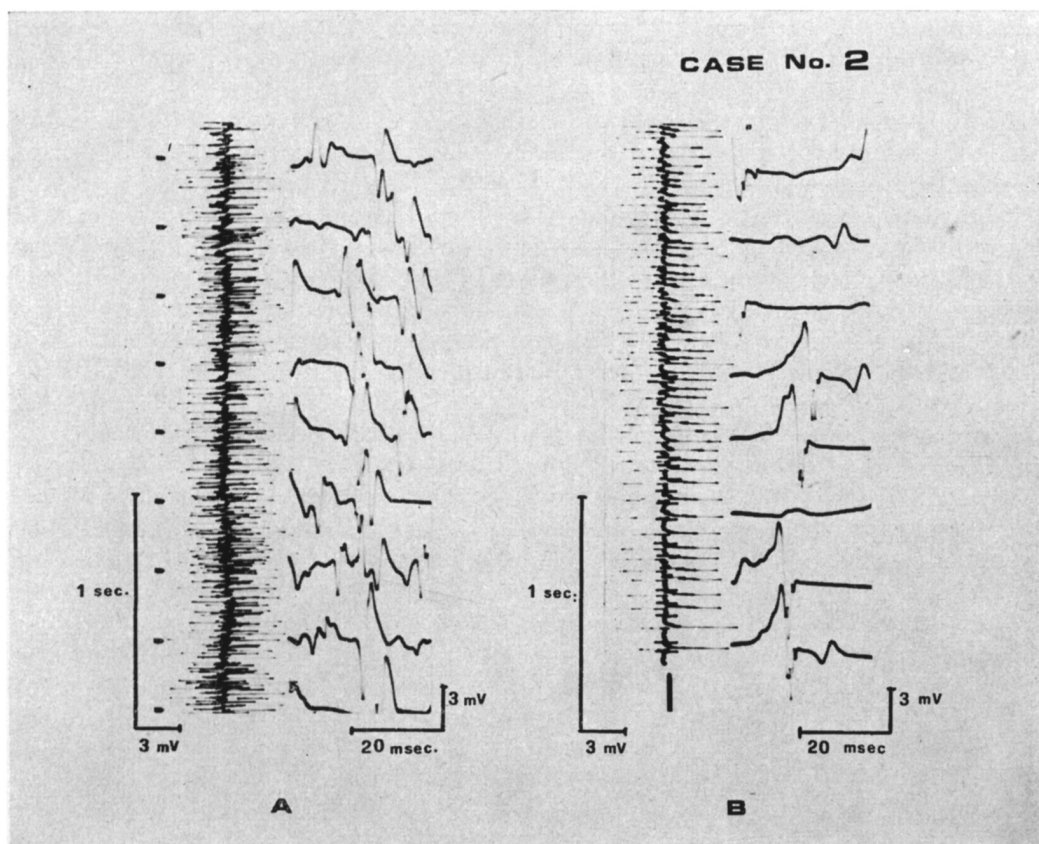


Fig. 7. Case No. 2: electromyographic recordings from the first interosseus of the left hand (A) and the right quadriceps (B). In this case, too, reduced interference on maximal contraction is present, as well as increased duration and amplitude of motor unit potentials.

EEG (Prof. C. Paolozzi): no abnormalities.

EMG (Prof. G. Sanna): first right interosseous and right quadriceps. On maximal contraction, reduced interference. Highly increased duration and amplitude of motor unit potential. No spontaneous activity (Fig. 7). Marked insertional activity. *Conclusions:* Neuropathic affection. Injury of anterior horn motor neurons.

Discussion

Evidence of spinal muscular atrophy in two siblings born from a consanguineous marriage, with onset in early infancy in one of them (V-6) and in adolescence in the other (V-5), again brings up the problem of whether Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander diseases are the same or distinct.

It should be pointed out that the mother of our probands (IV-8) was widowed and then married for the second time. She had no consanguinity with her second husband (IV-9). Of this marriage three children were born, all of whom are alive and healthy.

At the present time, no morphological, ultrastructural and, above all, biochemical criteria exist upon which an attempt at solving this problem can be based. Therefore, the most appropriate thing would seem to be the view of certain families affected with Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander diseases.

In this paper we do not deal with the problem of the so-called Werdnig-Hoffmann *abortive* forms, namely those subjects descending from families affected with Werdnig-Hoffmann disease with a marked delay in gait acquisition but with no detectable, subsequent dysfunction. This problem has already been brought up by Hanhart (1945) and by Brandt (1950). A very significant and pertinent family has been described by Thieffry et al (1955).

Nor do we discuss the problem of *nonprogressive* forms of spinal muscular atrophy, with congenital onset (family described by Lugaresi et al, 1966), or with infantile onset (family described by Magee and De Jong, 1960) followed by a prolonged course until adult years and even until middle life.

Finally, we shall not consider here random or familial cases of chronic poliomyelitis with late onset.

Our present study relates exclusively to forms of infanto-juvenile familial spinal progressive muscular atrophy.

First, let us examine a group of families affected with Werdnig-Hoffmann disease which can be referred to as "classic forms": *the disease is present at birth or it appears in the early months of life and death occurs within the first year of life.* Typical instances of this *group A* are families III, IV, VI, VII, X, XXVII, XXVIII, and XXXII, described by Brandt (1950); the Van Go... family, described by Radermecker (1951); and certain families studied by Thieffry et al (1955).

In *group B* we include those families in which *onset occurs within the first year of life, but the course is far slower.* These cases are often indicated in pertinent literature as

Werdnig-Hoffmann disease with prolonged course. In the two siblings (cases 34 and 35) described by Byers and Banker (1961) the first symptoms appeared when they were 6 months old: they were still alive at the age of 30 and 42 months when the paper was drawn up. Byers and Banker also quote the case of a family in which two cousins were affected (cases 33 and 36): the first symptoms appeared at the age of 6 and 8 months, and the cousins were still alive at 34 and 30 months, respectively.

In family II by Martin-Sneessens (1962) patients had been examined by Dr. van Bogaert until the age of 10, 13, and 17.

Cases 9 and 19 by Gamstorp (1967) are two siblings. The former was affected at birth, the latter at the age of 10 months: both were still alive at 12 and 11 years, respectively.

In case I by Greenfield and Stern (1927) the disease was present at birth and the patient died at 13 years of age. His younger brother was also affected; the authors, however, do not report the age of onset.

In family 14 by Peters et al (1968) one subject died at 11 years of age and his brother at 18. In family 16 one subject died at 15, while another of his brothers, also affected, was still alive at 10.

An intermediate group (group C) — with cases of Werdnig-Hoffmann disease with early onset and malignant course (group A), as well as cases of Werdnig-Hoffmann disease with early onset and prolonged course (group B) — also exists in the same family.

The family described by Krabbe (1920) could be included in this group: the patient (case no. 5) died at 4 months and an aunt of hers died at 8 years of age. The data reported by Krabbe clearly indicate that the first patient was affected with Werdnig-Hoffmann disease, while insufficient information was available concerning her aunt.

One of the families described by Thieffry et al (1955) is more representative: one of two siblings died at 10 months, while the other was still alive and 5 years old when the paper was being published.

Other typical instances of this group are families 3, 4, and 6 by Hausmanowa-Petrusewicz et al (1966); family 26 by Peters et al (1968); and families of cases 4, 14, 17, and 18 by Munsat et al (1969).

The family described by Dubowitz (1964: cases no. 4, 5, and addendum) may also be included in this group: in one subject the disease appeared at 6, followed by death at 23 months of age. Two sisters could never stand or walk, and were still living when the paper was published, at the age of 9 and 19 years.

Another group of families, similar to those described in group C, should be considered. In this group, cases of Werdnig-Hoffmann disease with early onset and subacute course (death within the first years of life), coexist with cases of Werdnig-Hoffmann disease with later onset (after the first year of life) and prolonged course.

The most significant instance is represented by the M. family by Gurdjian (1930): in one subject the disease was present at birth and death occurred at 3 years of age;

in his brother symptoms first appeared at 16 months, and he was still alive at 8 years of age.

In one subject of family XIV by Brandt (1950) onset was noted at 7-8 months, and death occurred at 2.9 years. Another subject, who had been affected since he was 18 months, died at 11 years.

In group C and the cases described above, there is evidence that, in the same sibship, the course of the disease is usually, though not always (Thieffry et al, 1955) identical.

A basic observation is the coexistence in the same family of congenital Werdnig-Hoffmann disease with both early and late onset in infancy with malignant, subacute and prolonged course. From the genetic point of view, this coexistence would seem to suggest the identity of these forms.

Apart from its nosological significance, this factor must also be taken into consideration by the clinician. The possibility that the disease appears in older (still healthy) siblings of affected subjects should never be excluded.

A similar remark may be made as regards Wohlfart-Kugelberg-Welander disease: "Heredito-familial juvenile spinal muscular atrophy simulating muscular dystrophy".

In none of the family cases these authors describe, is onset strictly juvenile. In all families some of the subjects have been affected since later infancy.

These Swedish authors have quite rightly drawn attention to forms with slight later onset, usually, but not always, with a more prolonged course.

Therefore, families affected with Wohlfart-Kugelberg-Welander disease can be subdivided into various groups.

Families with juvenile cases (onset during or immediately after puberty) are included in group A.

The most typical family in this group is that described by Castellotti and Scarlato (1966). In one subject onset was first noticed at 13 years, and in his brother at 20, and both were still living at 34 and 38 years of age.

Group B is far larger. It includes cases of progressive spinal muscular atrophies with onset usually occurring during the third infancy, or even during the second one, or at the end of early infancy. In all cases, the course of the disease is very slow.

In family IV by Kugelberg and Welander (1956: cases no. 7 and 8) the first symptoms of the disease appeared in two siblings when they were 3 years old, and both were still alive at the age of 26 and 23.

In family III by the same authors (cases no. 5 and 6) one subject was affected at 10 and the other at 3 years; both were still alive at 37 and 36.

In family 3 by Peters et al (1968) onset was noted in two siblings at 7 and 6 years of age, and they were still alive at 16 and 14. In family 9 by the same authors, symptoms appeared in two siblings at 7 and 3 years, and both were alive at 16 and 12. In family 10 by Peters et al (1968) the disease appeared in two subjects at approximately 5 years of age, and both were alive when 40 and 37 years old.

In family III by Martin-Sneessens (1962) onset in two subjects was noted at 7 and 4 years, and both were alive at 10 and 5, respectively.

In the family described by Spira (1967) one subject had been affected since he was 10 years old, another for as long as he could remember, and a nephew of theirs since he was 3 years old. All of them were still alive at 46, 30, and 20 years of age, respectively.

Here we also consider families with a slightly earlier onset (12-24 months).

In the Jul... family by Castaigne et al (1963) a young girl had been affected since she was 16-18 months old, and was still living when 14 years old. In her sister, onset was noted at the age of 1 $\frac{1}{2}$, and she was still alive at 9.

In family 7 by Peters et al (1968) a female subject had been affected since the age of 13 months, and was still living when 17 years old; in her brother, onset had been observed at 16 months, and he was still living at 35.

In family 8 by the same authors one subject had been affected since the age of 16 months, and he was still living when 17 years old. In his brother too, onset was noted at the age of 16 months, and he was still alive at 13 years.

Families in group C include cases with juvenile onset as well as subjects affected since infancy.

In family II by Kugelberg and Welander (1956) one subject had presented the disease since he was 17 years old, another since he was 3 $\frac{1}{2}$, and a third one since he was 2. All of them were still alive at 48, 12, and 17 years of age, respectively.

In a branch of family I by Wohlfart et al (1955) the first symptoms in a 23-year-old subject appeared at 2-3 years of age, whereas the earliest symptoms in a paternal cousin appeared at 14 years of age, and he was still alive at 26.

In family V by Kugelberg and Welander a female subject had been affected with the disease since she was 17, one of her brothers since he was 14, while another one had never walked normally. All of them were still alive at 57, 37, and 47 years, respectively.

Assuming that a clear distinction exists between Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander diseases, a number of families which cannot be included in any of the groups so far described must also be taken into consideration. These families are a separate group or may even be regarded, paradoxically, as cases of a new disease. In this group the same family includes both cases of Werdnig-Hoffmann and of Wohlfart-Kugelberg-Welander disease.

Heuyer et al (1946) describe two sisters aged 16 and 14: one had never been able to walk and the other began walking at 13 months of age, and symptoms of the disease first appeared when she was 3 years.

In a branch of family I by Wohlfart et al (1955) one subject, who had been affected since he was 3 months old, died at 10. His sister, aged 25, who had always been weak, has been affected since she was 10 years old.

In a subject of family II, by the same authors, the earliest symptoms appeared

when he took his first steps, and he was still alive at 18. A son of his brother had a marked hypotonia at 6 months of age: Werdnig-Hoffmann disease was diagnosed. Subsequently he got better: at 14 months he began walking, and at 4 years his gait was only clumsy.

Dunne and Chutorian (1966) report on three families: each of them had a child with spinal muscular atrophy during the first year of life; all subjects were still alive at 24, 46, and 72 months. In each of these families one sibling was able to walk, and the earliest symptoms were suspected at 11 months, 14 months, and 3 years, respectively. All of them were still alive at 4, 11, and 12 years of age.

In the sibship described by Sanna (1964) a small girl who had always been weak showed symptoms at 8, one of her brothers at 7, while in another the disease was present at birth. At the time of observation they were 11, 9, and 4 years old, respectively.

Family XXXIV by Brandt (1950) seems to be particularly noteworthy: a woman married twice and her two husbands were brothers. Among the children born of her first union, a female showed symptoms when she was 3 years old and died at 5, while another of her sons, who had been affected since he was 1 year old, died at 13. Among the children born from the second marriage, one female subject was never able to walk and died at 2 years of age; another had symptoms of the disease when 6 months old and was still alive at 18 years of age.

Family XIV by Brandt (and already quoted in group C of Werdnig-Hoffmann disease) can also be included in this group. Here the earliest symptoms of the disease were noticed in one subject when he was 7-8 months old, and he died at 2.9 years of age; in another, the age of onset was 18 months and death occurred at 11 years.

Observation 2 by Larbre et al (1965) is similar: in a child, aged 11, motor evolution had been normal and he was able to walk at 1 year of age. At that time, however, he began falling frequently. Later on, spinal muscular atrophy was diagnosed. One of his brothers died at the age of 22 months: his motor development had been far slower and he had not been able to stay in a sitting position until he was 15 months old.

The sibship described by Martin-Sneessens and Radermecker (1965) concerns a child who had been affected with spinal muscular atrophy since the age of 4 months, and who died when 27 months old. In his brother, who was 6 years old, motor development had been normal and the earliest disorders had occurred when he was 15 months old.

Case no. 7 by Radu et al (1966) concerns a female subject, aged 11, affected with spinal muscular atrophy since she was 6 years old. One of her sisters, who had been taken ill at the age of 9 months, died at 5 years of age; another one died of a similar disease at 6.

In family XXX by Brandt (1950) a woman, during her first marriage, mothered a child who became affected with spinal muscular atrophy since he was 7-8 years old, and was still alive at 20 years of age. A small girl, born from her second marriage, showed first symptoms at the time she should have been able to stand and walk.

She was already severely disabled at 18 months of age, and died when 5 $\frac{1}{2}$ years old.

A typical family is described by Amick et al (1966). In one subject, who was alive at 22 months of age, symptoms of the disease appeared when he was 8 months old; three of his uncles died, when they were between 2 and 4 years of age, of a disease characterized by muscular atrophy, weakness, respiratory disorders and tongue fasciculations. In another two of his uncles, who were twins, the disease appeared when they were 3 years old. Both were still living at 30 years of age, though they were confined to wheel chairs.

Families 8, 10, and 14 in the report by Hausmanowa-Petrusewicz et al (1966) contain subjects with spinal muscular atrophy with onset in the first year of life and a rapid fatal course, as well as subjects affected with the disease since they were 4 years old.

The mode of onset in cases no. 9 and 10 by Gardner-Medwin et al (1967) is the one most similar to that observed in our patients. One sibling was able to walk at 15 months but his gait had always been difficult. From 4 to 13 years of age he was still able to cycle, though he could hardly walk. Subsequently his conditions worsened and he has been living in a wheel chair since he was 27 years old. His brother had been healthy until he was 13 years old, successfully running in races. The earliest symptoms appeared at 15 years of age and at 33 the disease is still worsening.

Conclusion

The study of a family hitherto never described with two siblings with progressive spinal muscular atrophy (in one subject the disease has been present since his early infancy and in his sister since puberty) led us to examine a large number of families affected with Werdnig-Hoffmann or Wohlfart-Kugelberg-Welander diseases. A more detailed check has been carried out regarding subjects with different forms of the disease belonging to the same family.

Our paper does not deal with the problem of inheritance but concentrates on the intrafamilial aspects of the disease, and leads us to the following conclusions:

1) In infanto-juvenile progressive spinal muscular atrophy, early onset does not necessarily mean that the course will be malignant. Many opposite instances are to be found.

2) There is no doubt that in the same family the onset and course of the disease are usually similar for all affected subjects. Apart from abortive forms, which are not our main topic of discussion, we have noted in many families the coexistence of malignant Werdnig-Hoffmann disease, Werdnig-Hoffmann disease with a prolonged course, Wohlfart-Kugelberg-Welander disease with infantile onset, and Wohlfart-Kugelberg-Welander disease with juvenile onset.

3) We feel that the coexistence of all these different forms in the same family would seem to suggest that, from the genetic point of view, they should all be con-

sidered as clinical variants of the same disease. Only through the identification of distinct metabolic disturbances, will differentiation between various progressive spinal muscular atrophies with infantile and juvenile onset be justified.

4) A large number of cases with a greatly prolonged course should be grouped together with those forms, where usually, but not always, an earlier onset is noted. A comparative study should be carried out on these families and on the so-called non-progressive forms reported by Magee and De Jong (1960) and by Lugaresi et al (1966).

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RIASSUNTO

Studio clinico-genetico di due membri di una famiglia italiana, affetti da atrofia muscolare progressiva spinale. Il paziente di sesso maschile ha presentato i primi disturbi fin dall'infanzia e, per quanto gravemente invalido, è tuttora vivente all'età di 13 anni. Nella sorella, la sintomatologia è apparsa all'età di 15 anni circa ed attualmente la malattia sembra essere in rapida evoluzione. I pazienti sono figli di consanguinei. Da un secondo matrimonio non consanguineo della madre, rimasta vedova, sono nati altri tre figli, nessuno dei quali è ammalato.

Lo studio di questa famiglia, e di molte altre riportate nella letteratura, in cui sono presenti casi di atrofia muscolare spinale infantile accanto a casi ad esordio infanto-giovanile, porta alle seguenti considerazioni: (1) l'inizio precoce della malattia non comporta necessariamente un decorso maligno; (2) la malattia generalmente presenta caratteristiche di esordio e di decorso analoghe nei pazienti che appartengono ad una stessa famiglia.

In numerose famiglie esaminate è stata riscontrata la coesistenza di malattia di Werdnig-Hoffmann a decorso maligno con casi della stessa malattia, ma a decorso prolungato, o con casi di malattia di Wohlfart-Kugelberg-Welander, ad esordio sia infantile che giovanile.

Si ritiene, pertanto, che, almeno dal punto di vista genetico, tutte queste forme debbano essere incluse in un medesimo gruppo.

RÉSUMÉ

Étude clinico-génétique de deux membres d'une famille italienne atteints d'atrophie musculaire progressive spinale. Le garçon a présenté les premiers troubles dès l'enfance et, bien que sérieusement invalide, est toujours vivant à l'âge de 13 ans. Chez sa sœur, les premiers symptômes se sont présentés à l'âge de 15 ans environ

et la maladie paraît à présent évoluer rapidement. Les parents des deux sujets étaient consanguins; aucun des trois fils issus d'un deuxième mariage (non consanguin) de la mère, restée veuve, ne présente par contre pas la maladie.

L'étude de cette famille, ainsi que d'autres rapportées dans la bibliographie, caractérisées par la coexistence de cas d'atrophie musculaire spinale infantile et infanto-juvénile, conduit aux considérations suivantes: (1) un âge de début précoce n'implique pas nécessairement un cours malin; (2) le début et le cours de la maladie présentent généralement des caractéristiques similaires chez les sujets atteints d'une même famille.

La coexistence de la maladie de Werdnig-Hoffmann à cours malin avec des cas de la même maladie à cours prolongé, ou avec des cas de maladie de Wohlfart-Kugelberg-Welander à début infantile ou juvénile, a été remarquée chez de nombreuses familles.

Toutes ces formes pourraient donc, tout au moins au point de vue génétique, être comprises dans un seul groupe.

ZUSAMMENFASSUNG

Klinisch genetische Untersuchung von zwei Angehörigen einer italienischen Familie mit progressiver spinaler Muskelatrophie. Bei dem Knaben traten die ersten Störungen bereits in der ersten Kindheit auf, und obwohl schwer beschädigt, ist er heute mit 13 J. noch am Leben. Bei seiner Schwester zeigte sich der Symptomkomplex erst mit ca. 15 J. und augenblicklich scheint sich das Leiden rapid zu entwickeln. Beide sind Kinder aus einer Blutsverwandtenehe. Nach des Vaters Tod ging die Mutter eine neue Ehe ein, aus der drei Kinder hervorgingen, von denen keines krank ist.

Diese Untersuchung und ein Einblick in die im Schrifttum bekannten Fälle von spinaler Muskelatrophie sei es im Kindesalter als mit etwas späterem Auftreten führen zu folgenden Überlegungen: (1) das frühzeitige Auftreten muss nicht unbedingt einen malignen Verlauf des Leidens zur Folge haben; (2) bei Angehörigen einundderselben Familie sind Auftreten und Verlauf der Krankheit meistens ähnlich.

In vielen Familien fand man zugleich Fälle von Werdnig-Hoffmannscher Krankheit mit bösartigem Verlauf und andere von längerer Dauer sowie Fälle von Wohlfart-Kugelberg-Welanderscher Krankheit mit Eintritt im Kindes- oder auch im Jugendlichenalter.

Man nimmt daher an, dass alle diese Formen, wenigstens vom genetischen Standpunkt betrachtet, in einunddieselbe Gruppe einzugliedern sind.

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